REMARKS

Priority

The Examiner indicates that the application lacks a reference to the prior application. In response thereto, Applicants have amended the specification to properly recite that the instant application "is a continuation application of US Patent Application Serial Number 09/699,131, which was filed on October 26, 2000, and which issued as U.S. Patent No. 6,716,410 on April 6, 2004,..."

Applicants wish to point out to the Examiner that the replacement section with markings presented in the section entitled "**AMENDMENTS TO THE SPECIFICATION**" above, indicates changes to the text relative to the version of the section that was presented by Preliminary Amendment mailed November 11, 2003.

In reference to the priority claim, the Examiner has also pointed out that:

> "the specific reference to the prior application must be submitted during the pendency of the application and within the latter of four months from the actual filing date of the application or sixteen months from the filing date of the prior application." (Office Action, page 2.)

Further, the Examiner has indicated that this requirement is consider satisfied under the following circumstances:

> "if the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet 9ADS) as required by 37 CFR 1.78(a)(e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt,..." (Office Action, page 3.)

In response to this, Applicants submit herewith as Attachment A, a copy of the Utility Patent Application Transmittal that accompanied the instant application, indicating that it was a Continuation of U.S. Serial Number 09/699,131. Also, submitted herewith as Attachment B, is a copy of the first Filing Receipt mailed January 8, 2004, which indicates that a claim of priority to

U.S. Serial Number 09/699,131 was recognized by the Patent Office.

For these reasons, Applicants believe they have complied with the requirements for a claim to priority to U.S. Serial Number 09/699,131.

Information Disclosure Statement

The Examiner has indicated that the listing of references included in the specification is "not a proper information disclosure statement." Applicants wish to thank the Examiner for bringing this to their attention. In response to this, Applicants submit herewith an Information Disclosure Statement under 37 C.F.R. §1.97 including the three references listed in the specification that were not already included on the first two Information Disclosure Statements mailed on November 11, 2003 and March 29, 2004.

The Declaration

The Examiner has indicated that a new declaration is required due to an altered zip code for Inventor Witztum and a dual date entry for Inventor Palinski. In response to this, Applicants submit herewith for consideration a properly executed replacement declaration.

Rejection of Claims 34, 35 and 36 Under 35 U.S.C. §112, Second Paragraph

The Examiner has indicated that claims 34, 35 and 36 are "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." More particularly, the Examiner has indicated that claims 34 and 35 are vague and indefinite because of an improperly recited Markush group. Applicants submit herewith amendments to claims 34 and 35 in proper Markush group form. This amendment does not introduce new matter.

In reference to claim 36, the Examiner has indicated that this claim is indefinite in its recital of "plaques that are susceptible to rupture." In response, Applicants have amended claim 36 herein to recite the structure of such plaques as exhibiting "lipid pools exceeding 40% of the plaque area."

Support for this limitation is found in the specification on page 2, line 21. Accordingly, no new matter is added.

Rejection of Claims 27, 30-42 and 44-45 Under 35 U.S.C. §112, First Paragraph

The Examiner alleges that claim 27, 30-42 and 44-45 are rejected under 35 U.S.C. §112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connection, to make and/or use the invention." In particular, the Examiner reasons that "[t]he claims and specification fail to provide the identity or structure of [the] antibody recognition site."

In addition, the Examiner alleges that the claims lack an adequate written description for failing to describe "the detailed structure of the infinite possible antibodies."

As amended herein, the claimed antibody (or fragment thereof) has four structural characteristics:

1) It is specific for oxidation specific epitopes found on copper-induced oxidized low density lipoprotein (Cu-OxLDL).
2) It is specific for oxidation specific epitopes found on malondialdehyde low density lipoprotein (MDA-LDL).
3) It does not bind to native LDL.
4) It inhibits uptake of Cu-OxLDL by macrophages.

It would be well within the capacity of a person of skill in the art to select antibodies on the basis of meeting these criteria based on the teachings included in the specification. Such antibodies are thought to function by blocking uptake of OxLDL by macrophages which inhibits the formation of foam cells (page 18, lines 32-33.) The exact structure of such selected antibodies and their binding sites could easily have been determined based on the level of skill in the art know at the time of filing based on routine high-throughput screening experiments.

The Examiner bases the alleged requirement that "[t]he nucleic acid structure is required" to meet the written description requirement on *Fiers v. Revel,* 25 USPQ 2d 1601 at 1606 (Fed. Cir.

1993) and *Amgen v. Chugai Pharmaceuticals Co., Ltd.*, 18 USPQ 2d 1016 (Fed. Cir. 1991).

The court held in *Fiers* that, "what is needed to meet the description requirement will necessarily vary depending on the nature of the invention claimed." (*Fiers, supra,* at 1170.) In *Fiers* and in *Amgen,* the claimed invention was a DNA encoding a particular protein. In contrast, the instant invention is a method of using an antibody having specifically enumerated structural characteristics. Applicants request the Examiner to consider that antibodies are not the same as nucleic acids in terms of what is necessary to establish that they are adequately described under 35 U.S.C. §112, first paragraph.

In further support of this ground for rejection, the Examiner recites that "[t]he instant specification and claims describe an isolated monoclonal antibody by its protein function, however this description does not describe the claimed antibody itself. See also, *In the [Regents] of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412,...)(1997). Again, the Examiner is citing cases holding that claims to DNA were unpatentable as lacking an adequate written description.

In two more recent court decisions, the patentability of antibodies has been reviewed. In *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004), the claims at issue were directed towards monoclonal antibodies that targeted the CD40CR antigen expressed by activated human T cells. In *Noelle*, the Federal circuit stated, "the PTO would find compliance with 112, 1, for a claim to an isolated antibody capable of binding to antigen X, notwithstanding the functional definition of the antibody, in light of the well-defined structural characteristics of antibody binding, and the fact that the antibody technology is well developed and mature" (*Noelle, supra,* at 1349 (quoting *Enzo Biochem v. Gen-Probe, Inc.*, 323 F.3d 956, 970 (Fed. Cir. 2002).) In *Noelle,* claims which recited a genus of antibodies that bound to a mouse antigen were found to be unpatentable, because the corresponding human antigen had not been adequately characterized. However, in the instant case, the characteristics of the antigen are specified – the antigen is found on CuOxLDL, MDA-LDL, but not on normal LDL, and the antigen is recognized by macrophages. It is not necessary that the antigen be characterized to the level of amino acid sequence, since modern techniques of high throughput screening and molecular modeling could have easily been employed to do so at the time

the application was filed. In fact, even as early as 1997, epitopes on the surface of macrophages that bind to OxLDL were well known in the literature. See Attachment C hereto.

The Examiner additionally opines that the Applicant "provides no guidance as to what modifications or structure are important for the predictable function of the monospecific antibody." However, Applicants submit that this standard is presently too harsh, given the advances in technology since the cases that the Examiner is relying on were decided. As recited above, the court in *Noelle* held that the PTO would find compliance with the written description requirements for a claim to an antibody capable of binding to a particular antigen, "in light of the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature" (*Noelle, supra*, at 1349.) Accordingly, Applicants respectfully request reconsideration of this position.

In conclusion, Applicants submit that claim 27, and all of the claims dependent thereon, are adequately enabled and described in the instant specification.

Double Patenting

The Examiner finds that the instant specification is subject to a double patenting rejection over claims 1-19 of U.S. Patent No. 6,716,410 (the '410 patent) and claims 1-7 of U.S. Patent No. 6,375,925 (the '925 patent.) Applicants submit herewith a terminal disclaimer to the '410 patent. However, Applicants respectfully disagree with this ground for rejection over the '925 patent.

The '925 patent describes and claims antibodies that bind to specific epitopes of MDA2 and NA59 in plaque. These are "oxidation-specific epitopes" in oxLDL (col. 4, lines 25-39.) These epitopes are completely different. MDA2 antibodies target malondialdehyde-lysine, and NA59 antibodies target 4-hydroxylnonenal(4-HNE)-lysine (col. 5, lines 1-5.) Accordingly, although they are each described as demonstrating "binding characteristics which are almost identical" (col. 5, line 29), their specificity is entirely different. Moreover, the antibodies of the present invention that cross-react with both MDA-LDL and Cu-OxLDL do "not bind significantly to 4-HNE-LDL. Accordingly, the presently claimed antibodies are entirely different from the antibodies described and claimed in the '925 patent. As amended herein, the claimed antibodies are neither taught nor

suggested by the '925 patent. Indeed, the '925 patent is directed towards the production of antibodies that are specific for a single epitope on an oxLDL – this teaches away from the production of an antibody that cross reacts with two or more epitopes as is presently claimed.

The Examiner further reasons that claims 31 and 32 are unpatentable over the '925 patent in further view of Tsimikas et al. (*Journal of Nuclear Cardiology*, Vol. 6, Number 1, pages 41-53, Jan/Feb 1999, part I ("Tsimikas".) However, this reference goes no further than the '925 patent alone. It merely describes the further characterization of the MDA2 antibody. Accordingly, for the reasons stated above that the '925 patent teaches away from the instant invention, this combination of references also does not render obvious any of the claims as amended herein.

Rejection Under 35 U.S.C. §102(e)

The Examiner has indicated that claims 27, 31 and 34-35 are unpatentable under 35 U.S.C. §102(e) over Witztum et al., U.S. Patent No. 6,225,070 ('070.) More particularly, the Examiner reasons that the mouse monoclonal antibodies, E06, E013, E014 and E017, anticipate the recited claims.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. MPEP 2131, citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The monoclonal antibodies that are claimed and described in the '070 patent are produced in apolipoprotein deficient mice. They all have differential binding to LDL associated epitopes, but none is selected to be specific for MDL-LDL and Cu-OxLDL. Any cross-reactivity between antibodies is merely incidental, and does not constitute "specificity".

For example, E06 is characterized as being specific for Cu-OxLDL, but is also shown to bind to MDA-LDL, but only if it is greater than 70% oxidized. Also, E06 is shown to bind to native LDL (Table I). As indicated in Table II, E06 is best used as a determinant of circulating LDL, whereas the antibodies of the present invention are targeted towards plaques. The other antibodies mentioned by the Examiner (E013, E014 and E017) also have differential affinities for varying combinations of epitopes. However, none of the antibodies described or suggested in the '070 patent have the

specificities required by the instantly claimed invention. For this reason, the '070 patent does not anticipate the claimed invention.

Rejection Under 35 U.S.C. §103(a)

Claims 30-32, 36 and 38-42 are alleged to be unpatentable under 35 U.S.C. §103(a) over the '070 patent in view of Tsimikas. More particularly, the Examiner indicates that Witztum fails to teach "imaging procedures that include a correlation between another site in the body not having atherosclerotic plaques and pathology evaluations of the atherosclerotic plaques," but such methods are rendered obvious over 070 in view of Tsimikas. For the following reasons, Applicants respectfully disagree with this ground for rejection.

"When an obviousness determination is based on multiple prior art references, there must be a showing of some 'teaching, suggestion, or reason'" to combine the references. *Winner International Royalty Corp. v. Ching-Rong Wang,* 202 F.3d 1340 (Fed. Cir. 1998), quoting *Gambro Lundia AB v. Baxter Healthcare Corp.,* 110 F.3d 1573 (Fed. Cir. 1997)(also noting that the "absence of such a suggestion to combine is dispositive in an obviousness determination.")

As previously discussed, the '070 patent does not teach or suggest every limitation of claim 27, which is the only independent claim in the instant application. As amended herein, claim 27 recites an antibody with a combination of four distinct structural characteristics, and this combination is absent from the '070 patent. Since Tsimikas is merely a more extensive characterization of one of the antibodies that is already well characterized in the '070 patent, it goes no further toward rendering claim 27 obvious than the '070 patent would alone. It is a well settled principle that if an independent claim is found to be novel and nonobvious over the prior art, the more narrow dependent claims must necessarily also be found to be novel and nonobvious over the same prior art.

Moreover, the '070 patent fails to suggest that one should select an antibody with the four recited structural characteristics of claim 27, and Tsimikas does not supply what is missing from the '070 patent. As recited in *Winner International*, obviousness cannot be found absent such a suggestion.

Claims 33, 34, 37 and 44-45 are also alleged to be unpatentable under 35 U.S.C. §103(a) over the '070 patent in view of PCT WO 98/21581 ('581.) More particularly, the Examiner indicates that the '070 patent does not teach administration of an antigen to reduce residual label, but that the '581 application teaches such a method. The Examiner concludes that, on this basis, the recited claims are obvious over the '070 patent in further view of the '581 application. However, just like Tsimikas, the '581 application is merely a further characterization of the MDA2 and NA59 antibodies that are already described in the '070 patent. Accordingly, this combination of references also fails to teach or suggest an antibody having the same combined characteristics as those recited in independent claim 27. For this reason, the recited claims cannot be obvious over this combination of references.

SUMMARY

If the Examiner believes that it would facilitate prosecution, Applicants' Attorney, Laurie A. Axford may be contacted at (619) 230-7714 or at laxford@gordonrees.com.

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Respectfully submitted,

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